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Synthesis of Macrocyclic Compounds

Part 1 — Depolymerization or Radical-Interchange Method

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Two general procedures are available for the synthesis of large rings—the depolymerization or radical-interchange method and the high-dilution method. Both of these are developments from the older process for the preparation of cyclic ketones, which involves heating the calcium salts of dibasic acids, but which is of value only in the formation of the lower members in which rings of 5 and 6 carbon atoms are formed.

Ruzicka extended the procedure to larger ring systems by utilizing the thorium, cerium, and yttrium salts of the appropriate dibasic acids to give many-membered cyclic ketones. However, for the most part only very poor yields were obtained. The actual ring formation is a slow reaction, and side reactions, such as polymerization to give linear polymers of large molecular weight, take place at a much faster rate.

Further research has resulted in two methods of controlling the products of this procedure. The first, depolymerization or radical-interchange, was applied by Carothers to the preparation of macrocyclic esters, anhydrides, and lactones. It is based on the principle that, in a series of mutually dependent and reversible reactions, constant removal of any trace of cyclic product will cause a displacement of the equilibrium, with the ultimate conversion of the entire sample into the cyclic product.

The second method, high dilution, has recently been employed by Ziegler in the synthesis of cyclic ketones. The principle involved in the procedure is that if a reaction takes place in a very dilute solution the possibility of two molecules meeting and reacting to form a polymer is diminished, since polymerization is favored by higher concentration.

Depolymerization or Radical-Interchange Method

The preparation of large rings by this method consists of depolymerizing the corresponding linear polymers which are first formed. The esters obtained by the reaction of glycols and alkyl carbonates, for example, are linear polymers with molecular weights of 3000-5000. Polyesters of this type have been prepared from glycols and different dibasic acids, such as carbonic, oxalic, malonic, succinic, etc. When these are heated in a high vacuum with a condenser placed close to the evaporation surface, as in a molecular still or, in some cases, merely in a distilling flask, they undergo trans-

formations as summarized in the reaction scheme that is shown as Figure 1. The β-product collects on the condenser

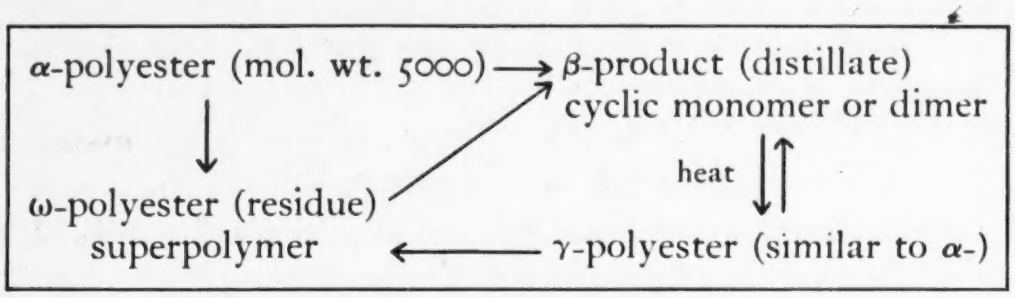


FIGURE 1—*Depolymerization of linear polymers.*

and the residue increases progressively in viscosity and molecular weight. The resulting ω-polyester depolymerizes just as the α-polyester, and, if the heating is continued long enough, complete conversion to the β-form finally occurs. The β-products, when heated or allowed to stand, readily go over to the γ-polyesters which have the same physical properties as the α-polyesters but, at least when freshly formed under anhydrous conditions, are perhaps giant rings.

The depolymerization effected by internal re-esterification is illustrated by the equation shown as Figure 2.

The success of this method depends on many factors, the two most important being the nature of the polyester and the use of catalysts. The esters of carbonic and of oxalic acids depolymerize more readily and smoothly than any others—merely by heating them in the presence of a catalyst under diminished pressure in an ordinary distilling flask. The

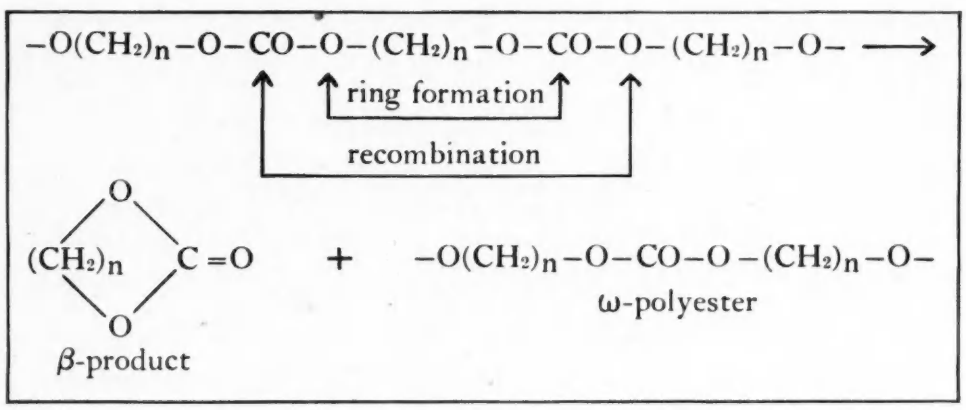


FIGURE 2—*Internal re-esterification.*

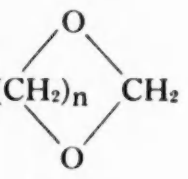
materials which act as effective catalysts with esters of the higher dibasic acids are all inorganic salts. The esters give crude yields of 40-85%. Presumably both mono- and dimers are present in the crude distillate. For unit lengths of 8, 9, 10, or 11 atoms, dimers predominate; above 13, little or no dimer is formed. The ratio of di- to monomer can be varied by choice of catalyst and operating conditions.

Cyclic anhydrides are obtained in a similar manner from linear polymers prepared by the action of acetic anhydride or acetyl chloride on dibasic acids.

The formals comprise another group of linear polymers and large rings. When a glycol and dibutyl formal are heated in the presence of an acidic catalyst, an acetal interchange results—

$$HO(CH_2)_nOH + BuOCH_2OBu \longrightarrow -CH_2O(CH_2)_n-O- + 2BuOH$$

When the α-polyformals are heated at low pressure in a still, conversion to the β- and ω-forms occurs. The β-forms constitute a new type of large rings, as represented at the right.



The method has also been applied to the preparation of lactones. The possibilities are indicated by the fact that a 70% yield of the pure monomer has been obtained from hydroxytetradecanoic acid.

The monomeric cyclic anhydrides, lactones, carbonates, malonates, oxalates, etc., have characteristic odors; for example, in some of the higher members, they closely resemble that of musk. The odors are rather vague and indefinite until the number of atoms in the ring reaches 9; a camphoraceous or minty quality then appears, and at about 13 a woody or cedarlike fragrance becomes apparent. Beyond this

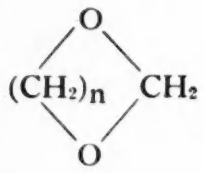
there is a musk which, in the anhydride series, however, does not become definite until 15. At 15 and 16 the musk quality approaches a maximum of fullness and homogeneity, being most noticeable in the lactones, carbonates, ketones, and ether lactones. Beyond 18 or 19 the odors in each series practically disappear.

The structural feature common to each series is the presence of one or more carbonyl groups as a member of the ring. From the practical standpoint the cyclic anhydrides are of no interest as odorous materials, since they polymerize spontaneously on standing and become odorless. On the other hand, the cyclic esters, with the exception of the oxalates, are quite resistant to hydrolysis or polymerization and have an advantage over the previously described ketones and lactones in that they are formed in relatively high yields.

The foregoing would suggest that the only requirement for a musklike odor is the presence of a carbonyl group in a ring consisting of about 15 atoms. However, Ruzicka has observed that the cyclic imine,

$$\ulcorner (CH_2)_{16}-NH \lrcorner$$

has a similar odor, thus demonstrating that the presence of a carbonyl group is not necessary. The odors of the cyclic formals, right, point to the same conclusion.



Any discussion of large rings secured by the depolymerization method would not be complete without the inclusion of rings containing a benzene nucleus linked through the meta and para positions. The formation of such cyclic systems has been one of the conventional problems of organic chemistry which have long resisted solution.

Carothers has employed this method in the preparation of such compounds. The acids m- and p-$C_6H_4(OCH_2COOH)_2$ were esterified with glycols of the series $HO(CH_2)_nOH$ and the resulting polyesters depolymerized. In this manner were obtained m-rings of 13, 14, 15, 17, 20, and 21 atoms in a 16-35% yield and p-rings of 16, 18, and 22 atoms in a 12-18% yield, of the types shown in Figure 3. The failure to procure by this means m-rings smaller than 13 atoms and p-rings smaller than 16 atoms would suggest that these are not likely to be obtained, but this is in no way conclusive.

Ruzicka prepared similar products by application of the thorium salt method to p-$C_6H_4(CH_2)_5COOH)_2$, and likewise to m-$C_6H_4(CH_2)_6COOH)_2$, and from the latter

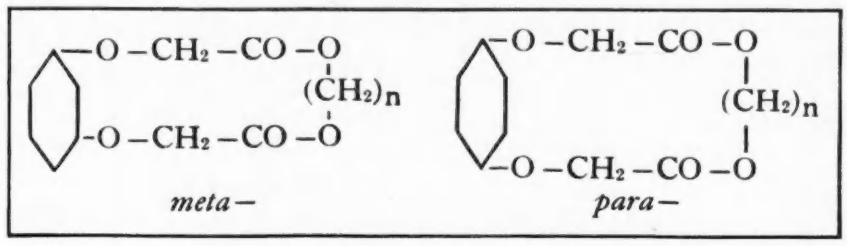


FIGURE 3—*Meta and para rings.*

obtained small amounts of a 16-membered ring. Recently Ziegler applied the high-dilution principle to the nitriles, m- and p-$C_6H_4(O(CH_2)_6CN)_2$, and formed in good yield the cyclic iminonitriles of 18 and 19 atoms.

The fact that the odor of musk is perceptible in 16-membered m- and p-rings, such as resorcinol decamethylene ether, further supports the theory that the only requirement for a musklike quality is a ring of suitable size.

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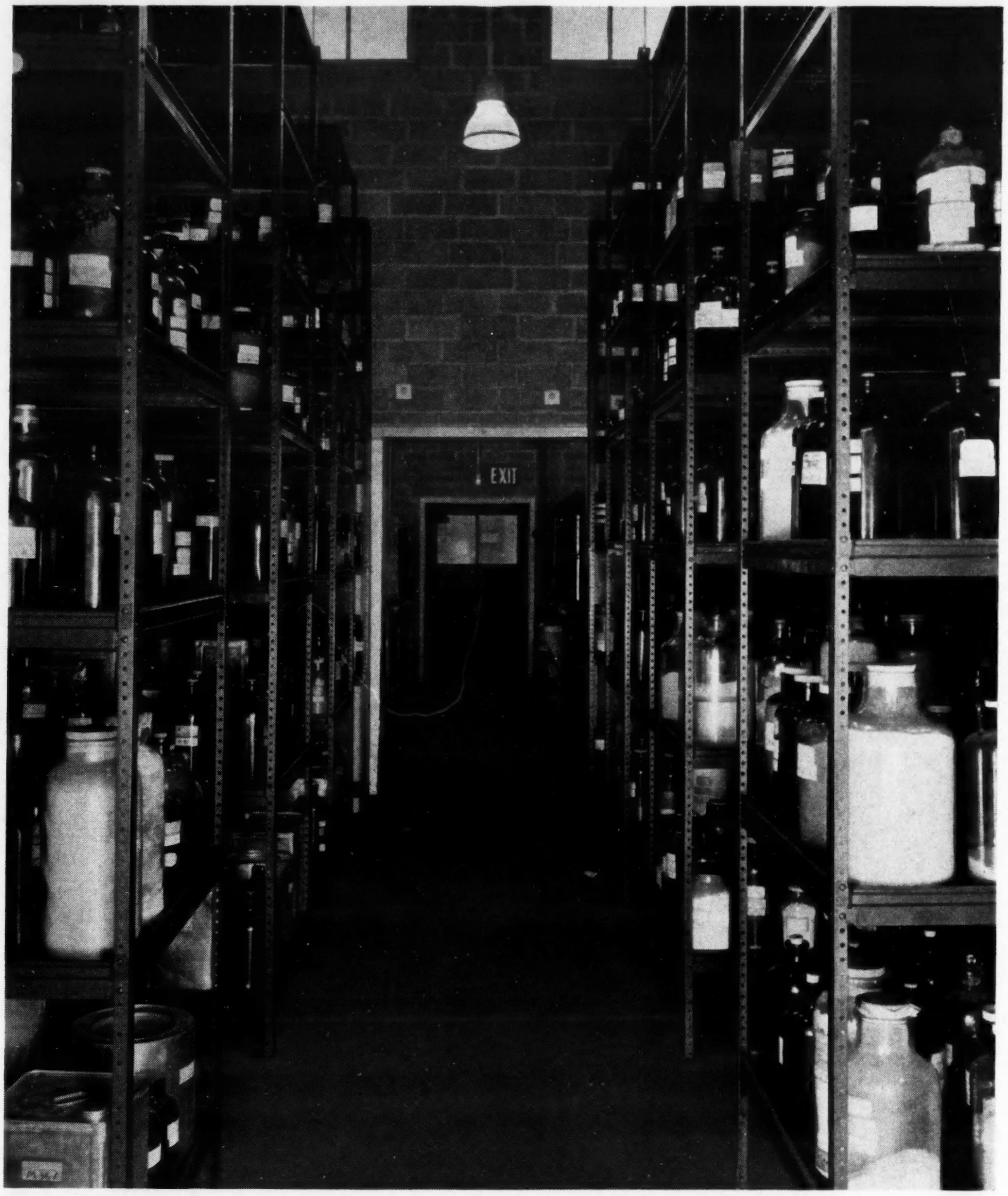

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